doi:10.2533/chimia.2020.18 Chimia 74 (2020) 18–22

Cascades, Catalysis and Chiral Ligand Control with SmI_2; The Rebirth of a Reagent

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Abstract: This review focuses on recent developments from our laboratory in the field of radical reactions mediated by the archetypal reductive single electron transfer (SET) reagent, SmI_2. Namely, we have expanded the scope of reducible carbonyl moieties to esters and amides and have exploited the resultant ketyl radicals in radical cascade reactions that generate unprecedented scaffolds. Moreover, we have taken the first steps to address the long-standing challenges of catalysis and chiral ligand control associated with the reagent.

Keywords: Enantioselective desymmetrisation · Radical cascade · Radical relay catalysis · Samarium diiodide

Áron Péter received his BSc degree from the Eötvös Loránd University (Hungary) in 2018. He completed his thesis work in the Servier Research Institute focusing on the synthesis of biologically active scaffolds. He then moved to the University of Manchester to conduct his MSc studies under the guidance of Professor David J. Procter on the use of SmI_2 in total synthesis. Following this, he received a prestigious Dean's Award to study for his PhD in the Procter group. His current research is focused on the development of new processes mediated by SmI_2.

Professor David J. Procter was born in Leyland in Lancashire, England. He obtained his BSc in Chemistry from the University of Leeds in 1992 and his PhD in 1995 working with Professor Christopher Rayner on organosulfur and organoselenium chemistry. He then spent two years as a Postdoctoral Research Associate with Professor Robert Holton at Florida State University in Tallahassee, USA working on the synthesis of Taxol. In late 1997 he took up a Lectureship at the University of Glasgow in Scotland and was promoted to Senior Lecturer in 2004. In 2004, he moved to a Readership at the University of Manchester. David was promoted to Professor in 2008 and is currently an EPSRC Established Career Fellow.

1. Introduction

In recent years, electron transfer processes have become increasingly popular for the formation of carbon–carbon bonds in synthetic organic chemistry.[1] In 1977, Kagan introduced one of the most important single electron reducing agents to the organic chemistry community: samarium(II) iodide.[2] The versatility of this commercially available reagent and its ability to combine radical and anionic processes has led to its widespread use over the past four decades.[3–5] In terms of carbon–carbon bond formation, SmI_2 has been successfully used in Barbier, Reformatsky, aldol, pinacol and, arguably, most importantly, carbonyl–alkene coupling reactions. Key to the above applications is the reagent's ability to activate alkyl halides, ketones and aldehydes, by reductive electron transfer, to form carbon-centred radicals. Furthermore, inorganic additives, proton sources, and Lewis bases may be used in conjunction with the reagent to fine-tune its reactivity and selectivity.[6] The unique properties of SmI_2 are unambiguously showcased in a wealth of total syntheses that utilise the reagent during their pivotal steps.[3,4]

2. The Key Challenges

Over the last decades, SmI_2-mediated reactions have been extensively explored making it one of the most important and widely-used single electron transfer (SET) reagents. Even though it remains popular amongst synthetic chemists, some drawbacks are associated with its use; for example, the scope of reducible carbonyl compounds is limited, most reactions use stoichiometric quantities of the reagent, and enantioselective reactions using chiral ligand control have proved elusive. Our group focuses on meeting these long-standing challenges in order to advance the field of electron transfer chemistry and to build a new future for SmI_2.

3. Cascade Reactions Mediated by SmI_2

Our team has not only expanded the scope of functional groups that can be activated by SmI_2 but has exploited these new reductions in selective cascades that deliver highly functionalised products. These cascades form natural product-like structures thus making complex targets more accessible. In 2018, we described a diversity-oriented synthesis of polycyclic systems bearing multiple stereocentres.[7] Simple, linear substrates can follow three different folding pathways triggered by reductive single electron transfer from SmI_2. Two of the radical cascade pathways utilise 1,5-hydrogen atom transfer (1,5-HAT) to activate secondary alkyl and benzylic groups whereas the third route generates complex lactones *via* an extended SET pathway (Scheme 1). The highly stereoselective formation of the key radical intermediates begins with a SmI_2-mediated Barbier cyclisation followed by an *in situ* lactonisation. The sequence continues with protic additive-promoted lactone radical cyclisations engaging unactivated alkenes in a 5-*exo*-trig fashion. Mechanistic studies using D_2O, as

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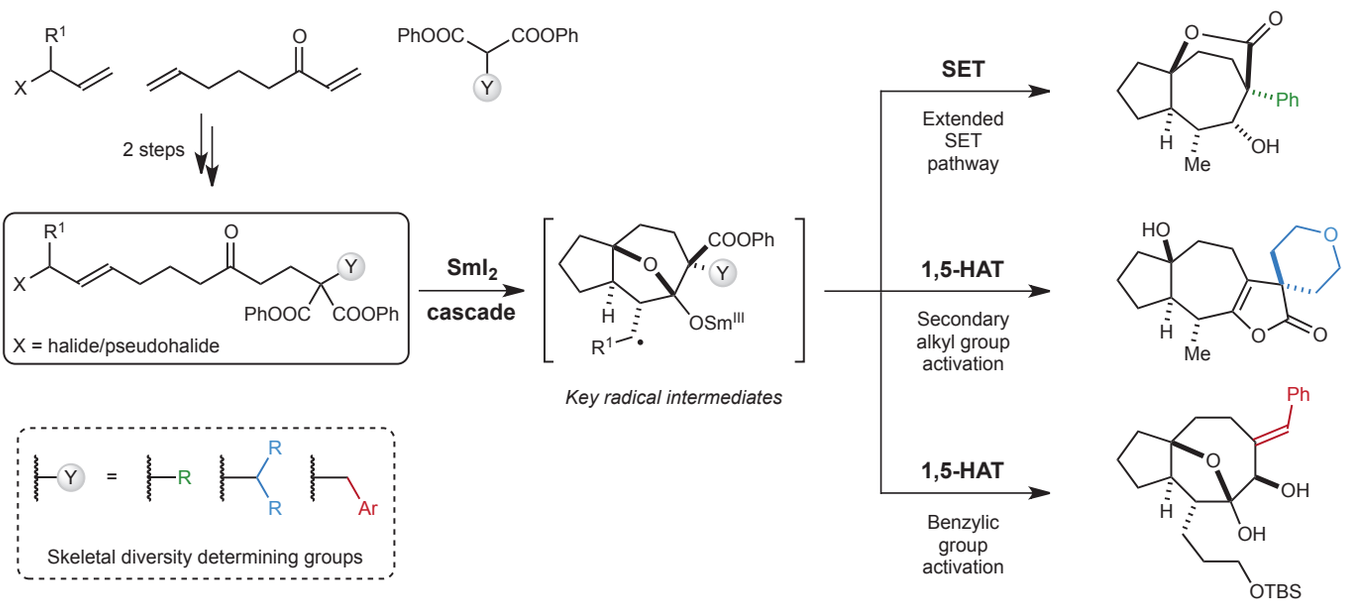
well as a deuterium labelled substrate, revealed that two folding pathways involve hydrogen atom transfer. Interestingly, 1,5-HAT rarely accompanies SmI_2-mediated reactions as the rate of reduction of radicals typically outcompetes the rate of hydrogen atom abstraction.[7] By careful substrate design, in which the resultant radical is formed in proximity to the site of abstraction, 1,5-HAT can be incorporated in diversity-oriented, radical, carbon–carbon bond-forming cascade reactions.

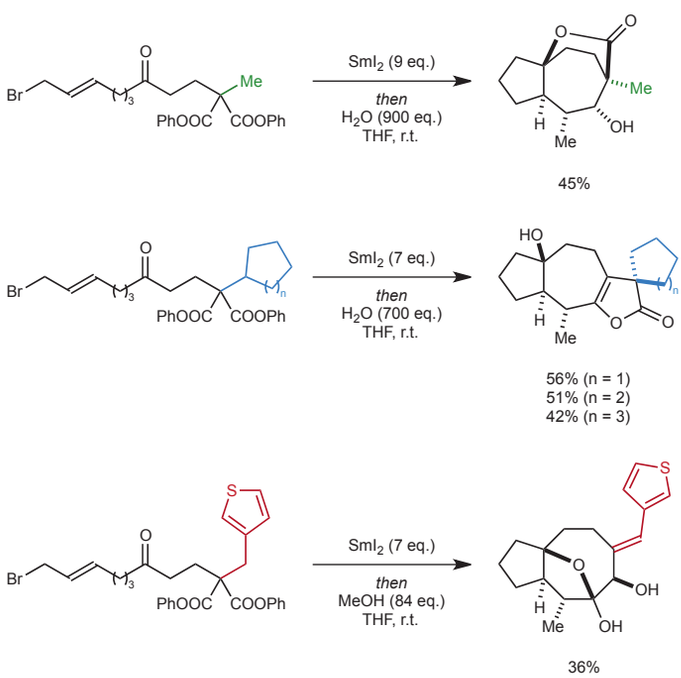
Several substrates were found to undergo folding with moderate to good yield delivering [5,7] and [5,8] fused bicyclic products (Scheme 2). In most cases the product is formed with complete diastereocontrol, a result of the coordination of Lewis basic sites in the substrate to the oxophilic samarium ion during folding.

The group has extended the radical–radical cyclisation cascade approach from cyclic esters[8] to the amide-type functionality in medicinally important barbiturates. The cascades allow unprecedented scaffolds to be generated with up to five contiguous stereocenters including quaternary stereocenters (Scheme 3).[9] These scaffolds feature readily manipulated polycyclic hemiaminal or enamine functionality that resemble motifs found in natural products. LiBr was shown to have a beneficial effect in reactions of the most challenging substrates presumably by forming $SmBr_2$, or the corresponding lithium ate species, *in situ* and consequently raising the redox potential of the reagent. In related studies, we have shown that this radical–radical cascade strategy can also be used in dearomatizing cyclisations to deliver polycyclic hemiaminals or enamines selectively from aromatic substrates.[10]

To further expand access to complex structures bearing a functionalised barbiturate core, the group developed alternative cascade reactions involving amide-type ketyl radicals.[11] Building on previous investigations which involved a carbocyclisation–heterocyclisation sequence (Scheme 3),[9,10] the group used the SmI_2–H_2O reagent system to trigger alternative heterocyclisation–carbocyclisation cascades. Symmetrical and unsymmetrical amide-



Scheme 1. A folding cascade strategy delivering [5,7] and [5,8] fused bicyclic architectures in a single step.



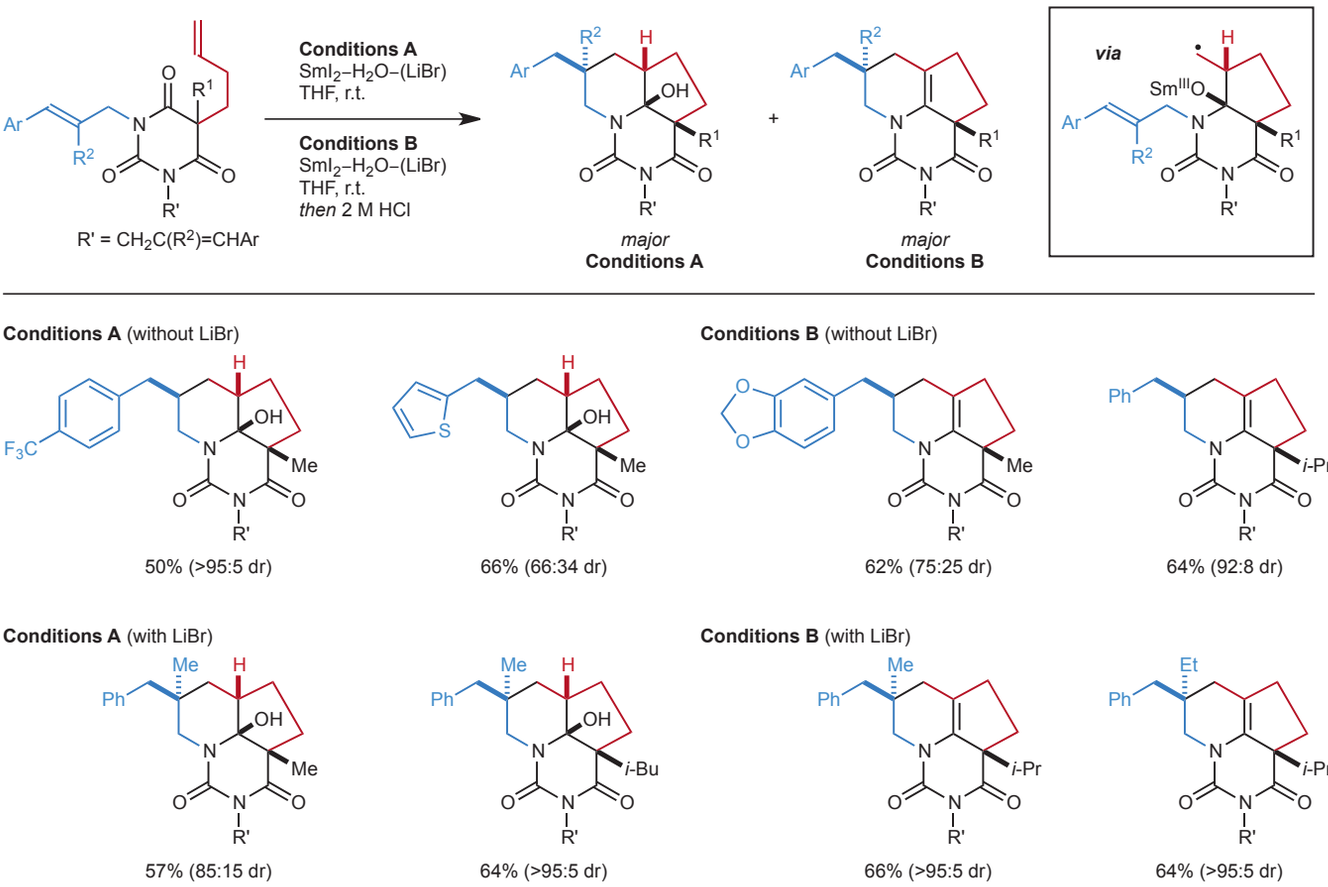
Scheme 2. Representative examples of a folding cascade strategy featuring ester–alkene radical cyclisations.

type substrates underwent the desired radical–radical cyclisation cascade reactions to give novel, complex tetracyclic products in good yield and with complete diastereocontrol (Scheme 4).

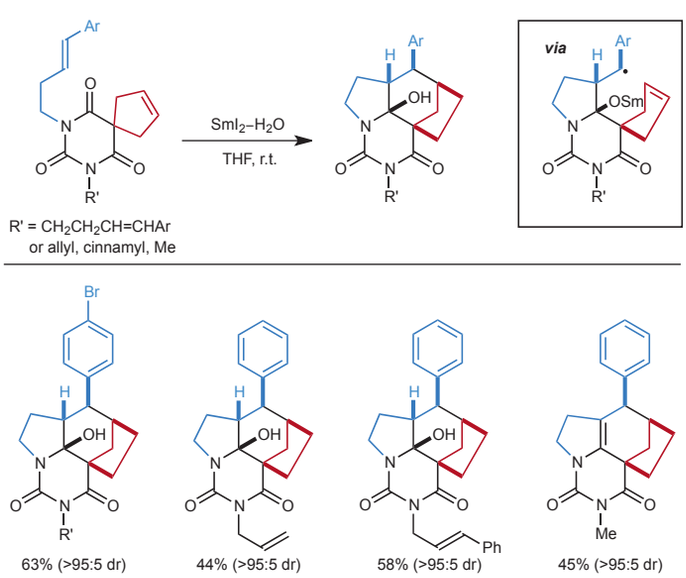
4. SmI_2-catalysed Cascade Cyclisations Enabled by Radical Relay

One of the major limitations of SmI_2 is that stoichiometric quantities of the reagent are almost always required. For example, in the simplest of SmI_2 reactions, after single electron reduction of a substrate, the resulting radical undergoes an intra or intermolecular reaction furnishing another radical that upon reduction, by another equivalent of SmI_2, and protonation, delivers the product.[6] Thus, such a process requires two equivalents of SmI_2. While the use of stoichiometric SmI_2 is often acceptable when the transformations are unique to the reagent, the development of catalytic SmI_2 reactions is an important goal. Some reports have shown that by employing super-stoichiometric quantities of a co-reductant, recycling of Sm(II) is possible and the reagent can be used in catalytic amounts.[12–14] For example, Zheng and Corey utilised Zn/Hg amalgam to turn over SmI_2 and to deliver, for example, spirolactones in good yield by an intermolecular ketone–alkene cross-coupling (Scheme 5A).[12]

Unfortunately, the use of a stoichiometric co-reductant, and the lithium halide and TMS triflate additives needed to recycle Sm(II),



Scheme 3. Representative examples of carbocyclisation–heterocyclisation cascades of barbiturates.



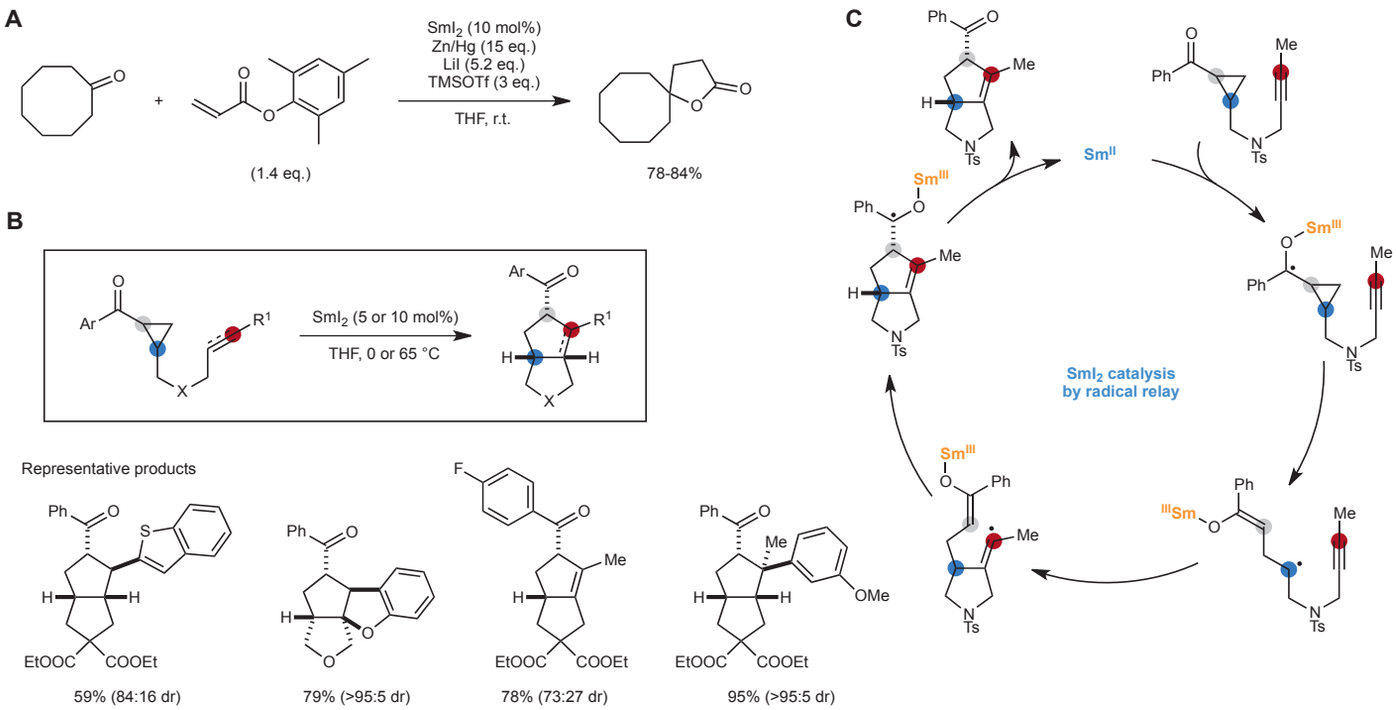
Scheme 4. Representative examples of heterocyclisation–carbocyclisation cascades of symmetrical and unsymmetrical barbiturates.

is far from ideal. As a result, systems such as this have not been widely adopted. The challenge to use SmI_2 as the sole catalytic mediator of cyclisations remained unmet until 2019 when we described the exploitation of a radical relay process that regenerates Sm(II) from Sm(III) (Scheme 5B).[15,16] In the catalytic approach, cyclopropyl aryl ketones are reduced and the resultant ketyl radicals undergo fragmentation to deliver carbon-centred radicals that are trapped intramolecularly (Scheme 5C). The resulting radicals rebound by addition to the enolate moiety, generating the [5,5] fused system. Electron transfer from the ketyl radical to the Sm(III) species closes the catalytic cycle and liberates the ketone product. The process is relatively broad in scope and tolerates the presence of esters, tertiary amines, bromides, functionalised aryl and heteroaryl rings, and delivers carbo- and heterocyclic products with high diastereocontrol. Furthermore, SmI_2-catalysed dearomatising cyclisations are also possible. Detailed density functional theory calculations, EPR studies, and mechanistic experiments support the proposed radical relay mechanism. It is hoped that this new approach can serve as a conceptual platform upon which other catalytic radical relay processes using the ubiquitous reducing agent, SmI_2, can be built.

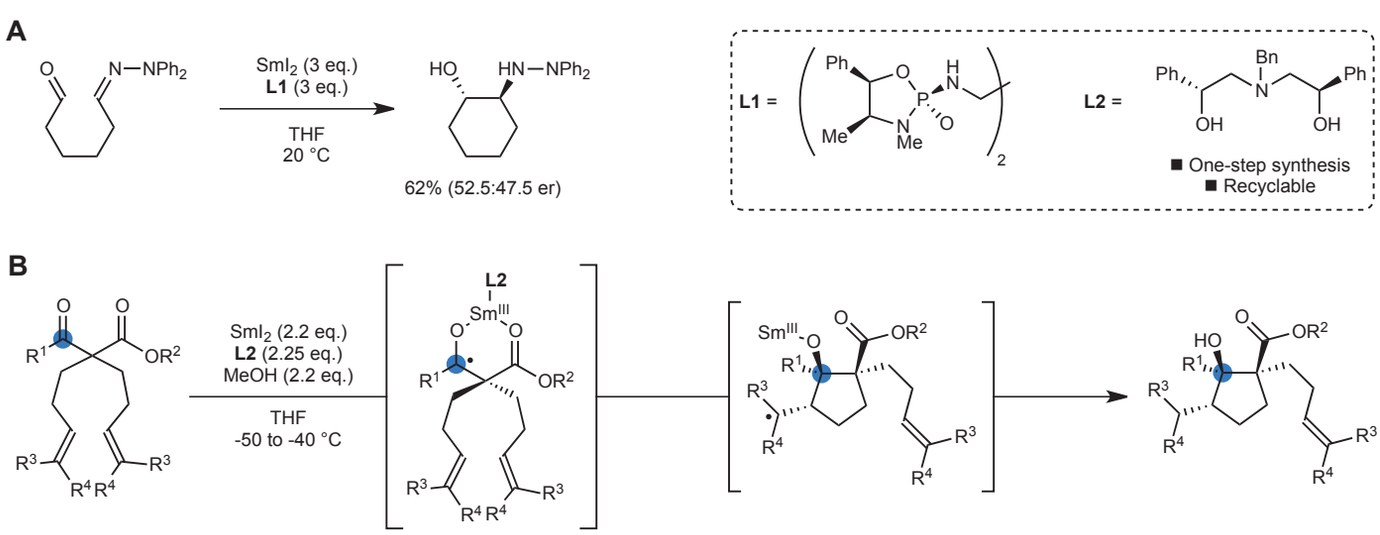
5. Enantioselective SmI_2-mediated Cyclisations and Cyclisation Cascades

SmI_2-mediated carbon–carbon bond-forming reactions are well known for the high diastereocontrol with which they proceed.[5] The oxophilic samarium(II) ion engages in intra as well as intermolecular coordination to Lewis basic sites in substrates delivering products with high control.[6] Unfortunately, attempts to use chiral ligands to control the enantioselectivity of SmI_2-mediated coupling reactions have met with little success. One isolated study published by the Mikami group in 1998 described the enantioselective, intermolecular, SmI_2-mediated coupling of acetophenones with acrylates using the chiral ligand (*R*)-BINAPO.[17] Examples of enantioselective intramolecular carbon–carbon bond formation using SmI_2 are even more scarce; for example, Skrydstrup and co-workers' attempted a SmI_2-mediated, pinacol-type cyclisation using an enantiopure bisphosphoramide ligand **L1**, however, little enantiocontrol was observed (Scheme 6A).[18]

Our development of enantioselective SmI_2-mediated processes exploits several design principles (Scheme 6B).[19] First, based on the work of Molander,[20] readily available dienyl β-ketoesters were selected as two-point-binding substrates for the development of enantioselective desymmetrising radical cyclisations. Second, a chiral ligand was selected that would

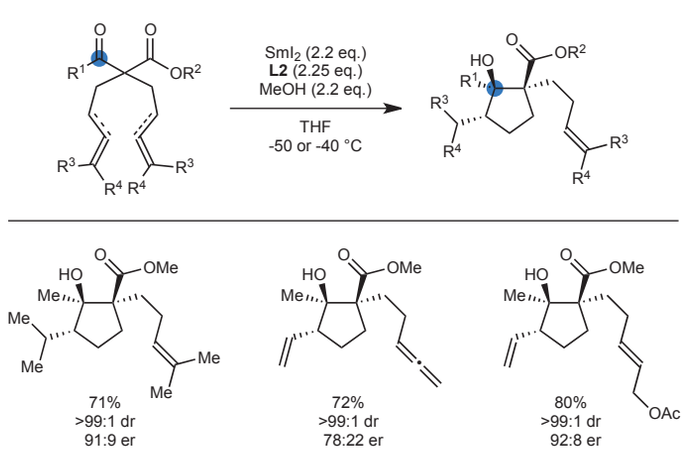


Scheme 5. Transformations using catalytic amounts of SmI_2. **A** The Corey method using superstoichiometric equivalents of a co-reductant to turn over SmI_2. **B** The SmI_2-catalysed transformation developed by Procter using cyclopropyl ketone substrates. **C** The proposed catalytic cycle highlighting the radical relay approach.

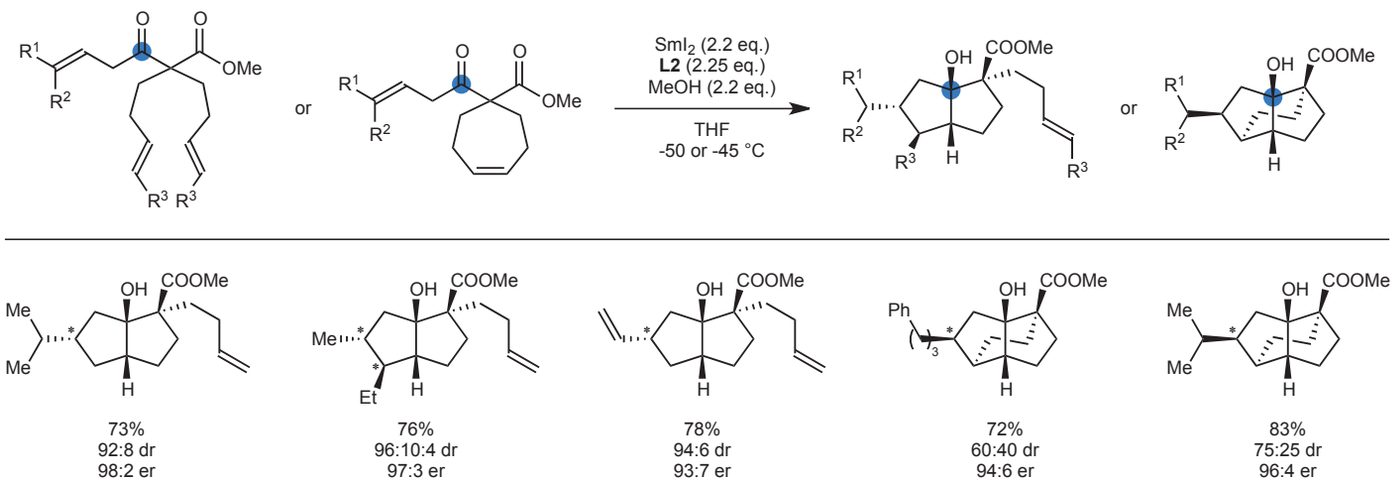


Scheme 6. Enantioselective cyclisations mediated by SmI_2. **A** Skrydstrup's system using a chiral bisphosphoramide ligand. **B** Enantioselective desymmetrisation using a tripodant aminodiol chiral ligand by the Procter group.

maximise the interaction between the chiral Sm(III) species and the substrate. In this regard, we moved away from the use of Lewis basic phosphoramide-type ligands, as cyclisations with closely related HMPA are thought to involve a solvent-separated ion pair.[21] Based on the known affinity of ethylene glycol for SmI_2,[22] we hypothesised that a flexible multidentate chiral diol could prove effective in controlling the enantioselectivity of cyclisations. Following extensive ligand screening, the team identified **L2** as the best ligand to facilitate enantioselective processes (Scheme 6). Both the temperature and the achiral protic additive played a crucial role in the reaction; the highest enantiocontrol and yield were observed when the reaction was carried out at –50 °C in the presence of 2.2 eq. MeOH. Methanol is thought to act as an additional ligand for samarium and as a quench for carbanionic intermediates, thus preserving the integrity of the chiral ligand. Pleasingly, the transformation proved to be general, generating a wide range of highly functionalised



Scheme 7. Representative examples of SmI_2-mediated enantioselective desymmetrising cyclisations.



Scheme 8. Enantioselective, SmI_2-mediated, desymmetrising radical cyclisation cascades. The asterisk highlights a centre at which diastereocontrol is not complete.

cyclopentane-containing products, typically with high diastereo and enantiocontrol (Scheme 7).

The team next sought to combine the radical cascade approaches previously explored in the group with chiral ligand control to deliver enantiomerically enriched products of high molecular complexity. To this end, cyclisation cascade substrates, bearing additional unactivated alkene radical traps, were synthesised and underwent reaction to give highly functionalised, fused bicyclic systems in good yield and with high enantio and diasterocontrol (Scheme 8).

6. Conclusion and Outlook

In summary, this review collates recent advances achieved by the Procter group in addressing key challenges associated with the use of one of the most important single electron reducing agents, SmI_2. New strategies have been developed in which unusual ketyl-radicals are generated from ester and amide groups in simple substrates and are exploited in reaction cascades that deliver complex, unprecedented, polycyclic architectures. Furthermore, SmI_2-catalysed cyclisation cascades have been developed in which a radical relay process is used to regenerate Sm(II). Finally, by employing a tripodant aminodiol chiral ligand, the group has reported highly enantioselective, desymmetrising cyclisation reactions mediated by SmI_2. The development of new enantioselective and catalytic cascade reactions that exploit this well-known reagent is ongoing in the group's laboratory.

Acknowledgement

We gratefully acknowledge funding from the UK Engineering and Physical Sciences Research Council (EPSRC; EP/M005062/01 – EPSRC Established Career Fellowship to D.J.P.) and the University of Manchester (Dean's Award to A.P.).

Received: November 26, 2019

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